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Prevalence of Thyroid Diseases in Nevada Counties With Respect to Perchlorate in Drinking Water

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Perchlorate is well-known to inhibit the uptake of iodine by the thyroid and has been shown to do so at doses in the milligrams-per-day range and higher. Perchlorate has been found in the water supply of Clark County (Las Vegas), Nevada, at 4 to 24 μg/L (parts per billion) and may provide exposure dosages in the tens of micrograms per day. An analysis of the Medicaid database from Nevada was undertaken to determine whether an increase in the prevalence of any thyroid disease was associated with that level of perchlorate content. The prevalence of persons being seen for thyroid disease or for specific thyroid diseases (goiter, nodule, thyrotoxicosis, congenital hypothyroidism, acquired hypothyroidism, thyroiditis, and other thyroid disorders) and for thyroid cancer among the Medicaid-eligible population of each county was calculated for the 2-year period 1997 to 1998. The prevalences in Clark County were compared with those in Washoe County (ie, Reno), the second most populous county in the state, and with those for the rest of the state. There was no evidence of an increased rate of thyroid disease (or of any specific thyroid disease) associated with perchlorate exposure. Generally, the prevalences in the metropolitan parts of the state were lower than for the rest of the state, particularly for acquired hypothyroidism. This analysis found no evidence that perchlorate-containing drinking water at the given level increased the prevalence of acquired hypothyroidism or of any other thyroid condition (J Occup Environ Med. *2001;43:630–634*)

Perchlorate, an inhibitor of iodine uptake by the thyroid, has been detected in the public drinking water in southern California in the range of 5 to 8 μg/L (parts per billion [ppb]) and in southern Nevada in the range of 5 to 24 μg/L. Studies examining whether these perchlorate exposures affected neonatal thyroid function found no increase in the prevalence of congenital hypothyroidism,[1] no decrease in thyroxine levels,[2] and no increase in thyroid-stimulating hormone levels[3] in the areas with perchlorate in drinking water compared with those without. We now extend this analytic model to adult thyroid disease to determine whether the prevalences of thyroid diseases are increased in the areas of Nevada that have perchlorate in the drinking water compared with those that do not. The current analysis examines Nevada Medicaid data for 1997 to 1998 to determine whether there is an effect of these perchlorate exposures over the full age range on the prevalence of thyroid diseases (International Classification of Diseases, 9th Revision [ICD-9], Codes 193 and 240 to 246) of the Medicaid-eligible residents of Clark County (which has perchlorate in the drinking water) and the Medicaid-eligible residents in the other counties without perchlorate in the drinking water.

Patients and Methods

The study population consisted of all users of the Nevada Medicaid program during the period of January 1, 1997, to December 31, 1998. Pa-

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TABLE 1
Thyroid Diseases and Their International Classification of Diseases, 9th Revision, Codes

Code	Diseases
193	Malignant neoplasm of thyroid gland
240	Simple and unspecified goiter
241	Non-toxic nodular goiter
242	Thyrotoxicosis with or without goiter
243	Congenital hypothyroidism
244	Acquired hypothyroidism
245	Thyroiditis
246	Other disorders of thyroid

tients were defined as those having one or more of the following diagnoses of thyroid disease: (1) simple and unspecified goiter (ICD-9, 240), (2) non-toxic nodular goiter (ICD-9, 241), (3) thyrotoxicosis with or without goiter (ICD-9, 242), (4) congenital hypothyroidism (ICD-9, 243), (5) acquired hypothyroidism (ICD-9, 244), (6) thyroiditis (ICD-9, 245), (7) other disorders of the thyroid (ICD-9, 246), or (8) malignant neoplasm of the thyroid gland (ICD-9, 193). The thyroid diseases and their ICD-9 codes are listed in Table 1.

The study data were extracted from the Nevada Medicaid database, from which personal identifiers had been removed. Each record was provided a patient study number so that all information on a given patient could be collapsed into a single record. Residential information was used to classify the exposure status of the study subjects. The state also provided a list of the number of persons eligible for Medicaid services by county for the mid-point of the study period. Those who resided in Clark County during the study period were considered exposed. Those who resided in the other Nevada counties (without perchlorate in drinking water) were considered unexposed. The thyroid diseases listed above were the outcomes of interest. The diagnosis of thyroid diseases (ICD-9, 193 and 240 to 246) was used to classify the outcome status of the study subjects.

The study population was categorized into three groups by county of residence (ie, Clark County, Washoe County, and other Nevada counties). Clark County is the most populous county in Nevada and has the city of Las Vegas as its major urban center. The water supplied to the city of Las Vegas is the same as that supplied to 96% of the residents of Clark County. Washoe County is the second most populous county in Nevada and has the city of Reno as its major urban center. The other counties in Nevada have no urban centers that approach the size of Las Vegas or Reno.

During the period July 1977 to June 1998, the perchlorate levels in the Clark County water ranged between 4.1 and 14 μg/L, with an average of 8.9 μg/L. No measurements were made before July 1997, and no perchlorate was detected between July 1998 and December 1998. The monthly average perchlorate level since 1998 has been 11.6 ppb. Using that as an estimate of the exposure levels before sampling, the average perchlorate level during 1997 to 1998 is estimated to be about 8 ppb. Perchlorate has never been detected in the public water supply of any area in Nevada outside of Clark County.

The prevalence of each of the eight thyroid diseases was calculated for each county and compared between Clark County and Washoe County and between Clark County and the other Nevada counties. The relative risk (prevalences) were calculated with 95% confidence intervals using EpiInfo. A chi-squared test with a two-tailed significance level of 0.05 was used for the comparison.

Results

A total of 176,847 eligible Medicaid users were in Nevada during the 1997 to 1998 study period. The frequency and prevalence of the eight thyroid diseases by counties and for the state are presented in Table 2. To reduce uncertainty in the point estimate, the counties with fewer than 2000 eligible users (n = 10) were combined into one analytic category. The prevalence for the eight thyroid diseases for Nevada ranged from 0.007% (for congenital hypothyroid-

TABLE 2
Frequency and Prevalence of Thyroid Disease by County In Nevada

		Goiter (240)*		Nodular (241)		Thyrotox (242)		Hypo-Con (243)		Hypo-Acq (244)		Thyroiditis (245)		Others (246)		Cancer (193)	
County	Eligible	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Clark	122,519	139	0.11	114	0.09	300	0.24	15	0.01	1445	1.18	49	0.04	47	0.04	28	0.02
Washoe	29,622	27	0.09	19	0.06	71	0.24	6	0.02	346	1.17	7	0.02	6	0.02	9	0.03
Carson	5,477	9	0.16	9	0.16	21	0.38	0	0.00	74	1.35	1	0.02	2	0.04	3	0.05
Nye	3,263	4	0.12	2	0.06	7	0.21	0	0.00	52	1.59	2	0.06	1	0.03	0	0.00
Elko	3,082	3	0.10	5	0.16	11	0.36	0	0.00	41	1.33	0	0.00	0	0.00	0	0.00
Lyon	2,968	2	0.07	1	0.03	7	0.24	0	0.00	39	1.31	0	0.00	1	0.03	2	0.07
Churchill	2,890	4	0.14	3	0.10	11	0.38	1	0.03	35	1.21	2	0.07	3	0.10	0	0.00
Others	7,026	4	0.06	4	0.06	19	0.27	0	0.00	114	1.62	3	0.04	3	0.04	2	0.03
Total	176,847	192	0.11	157	0.09	447	0.25	22	0.01	2146	1.21	64	0.04	63	0.04	44	0.02

* International Classification of Diseases, 9th Revision, code.

TABLE 3

Comparison of Thyroid Disease Prevalences in Clark, Washoe, and Other Counties in Nevada

County	Eligible	Goiter (240)*	Nodular (241)	Thyrotox (242)	Hypo-Con (243)	Hypo-Acq (244)	Thyroiditis (245)	Others (246)	Cancer (193)
Clark									
n	122,519	139	114	300	15	1,445	49	47	28
%		0.11	0.09	0.24	0.01	1.18	0.04	0.04	0.02
Washoe									
n	29,622	27	19	71	6	346	7	6	9
%		0.09	0.06	0.24	0.02	1.17	0.02	0.02	0.03
Other									
n	24,706	26	24	76	1	355	8	10	7
%		0.11	0.10	0.31	0.00	1.44	0.03	0.04	0.03
Clark vs Washoe									
RR†		1.24	1.45	1.02	0.60	1.01	1.69	1.89	0.75
95% CI		0.82–1.88	0.89–2.36	0.79–1.32	0.23–1.56	0.90–1.13	0.77–3.74	0.81–4.43	0.35–1.59
P		0.30	0.13	0.87	0.29	0.87	0.19	0.13	0.46
Clark vs other									
RR		1.08	0.96	0.80	3.02	0.82	1.24	0.95	0.81
95% CI		0.71–1.64	0.62–1.49	0.62–1.02	0.40–22.90	0.73–0.92	0.59–2.61	0.48–1.88	0.35–1.85
P		0.72	0.85	0.07	0.26	<0.001	0.58	0.88	0.61

* International Classification of Diseases, 9th Revision, code.

† RR, relative risk; CI, confidence interval.

ism) to 1.21% (for acquired hypothyroidism).

A comparison of the prevalences of each thyroid disease between Clark county and Washoe County, and between Clark County and other Nevada counties, was made as relative risks with 95% confidence limits and is presented in Table 3. None of the eight thyroid diseases significantly differed in prevalence between Clark County and Washoe County, with all relative risks being close to one (range, 0.60 to 1.89) (Table 3). None of the eight thyroid diseases prevalences was significantly higher in Clark County than in the rest of the state, and for acquired hypothyroidism the prevalence in Clark County (and in Washoe County) was significantly lower in the rest of the state (Table 3). Thus,

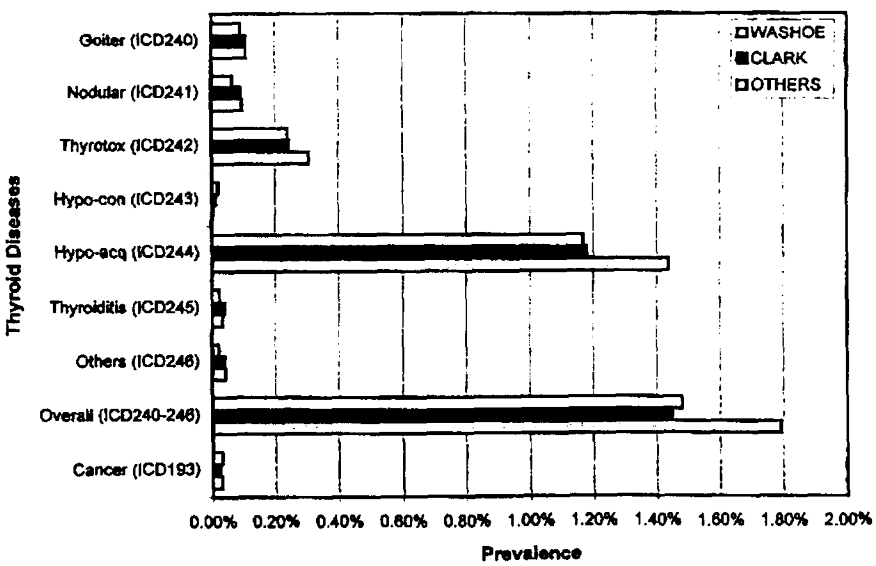

Fig. 1. Prevalence of thyroid disease (ICD-9, 240 to 246 and 193) by area, January 1, 1997, to December 31, 1998. Clark County is the area with perchlorate exposure.

in no case was the prevalence of any thyroid disease significantly greater in Clark County (which had perchlorate in the drinking water) than in Washoe County or the other counties that had no perchlorate in the drinking water.

The prevalence of the eight thyroid diseases by the three geographical areas (Clark, Washoe, and other counties) is presented in Fig. 1. For seven of the eight thyroid diseases, the prevalence in Clark County was lower than that in Washoe County or in the other counties (for thyroid cancer) or was in-between (for simple/unspecified goiter, non-toxic nodular goiter, thyrotoxicosis, congenital hypothyroidism, acquired hypothyroidism, and other disorders of thyroid). For thyroiditis (ICD-9, 245), the prevalence in Clark County was non-significantly higher than that in Washoe County or in other counties (P = 0.19 and 0.58, respectively).

The area-specific thyroid cancer prevalence pattern (0.02% in Clark County and 0.03% in both Washoe County and the rest of the state) seen here for 1997 to 1998 is similar to the thyroid cancer incidence pattern (5/100,000 in Clark County and

7/100,000 in both Washoe County and the rest of the state) seen for 1996 to 2000.

Discussion

This analysis compares the prevalence of eight thyroid diseases in Clark County with that in Washoe County and in other Nevada counties using Nevada Medicaid data for 1997 and 1998. A crude comparison showed that none of the eight thyroid diseases examined significantly differed in prevalence between Clark County and Washoe County. All but one thyroid disease (acquired hypothyroidism) showed no evidence of significant difference in prevalence between Clark County and the other counties. The prevalence difference was statistically significant ($P < 0.001$) for acquired hypothyroidism, with the prevalence of hypothyroidism being lower in Clark County than in other counties (contrary to expectation).

Of the eight thyroid diseases examined, the prevalence of acquired hypothyroidism (ICD-9, 245) was much greater than that of other thyroid diseases. A comparison across the state showed that the prevalence of acquired hypothyroidism in Clark County was located in the low prevalence zone as compared with that of the other Nevada counties (Fig. 2).

Age- and sex-adjusted prevalence could not be calculated because of the lack of information on age and sex distributions of the Medicaid-eligible population in each county. This analysis found no evidence that perchlorate-containing drinking water at the given level increased the prevalence of acquired hypothyroidism or any other thyroid condition.

Perchlorate is well-known as an anti-thyroidal agent and has been used to treat hyperthyroidism for about 50 years.[4] Today, it is the treatment of choice for hyperthyroidism caused by the iodine overload of amiodarone toxicity.[5] The therapeutic dosage for perchlorate is in the range of 100 to 900 mg/day.

The mechanism of action of perchlorate is clearly known as the competitive inhibition of the uptake of iodine by the sodium iodide symporter receptor site on the basolateral surface of the thyroidal cell.[6] The symporter has been cloned.[7] The original studies of the effect of perchlorate on Grave's disease patients showed that an oral dosage of 100 mg was sufficient to block the uptake of iodine and complete release of free iodine.[4] The same study showed partial effect at 30 mg and at 10 mg. A study of workers in perchlorate manufacturing demonstrated that groups of workers with inhalation and ingestion exposure showed no effect on thyroid hormone levels, even with an average daily absorbed dose of 34 mg/work shift.[8] Crump calculated from the data of this study a benchmark dose limit indicating a "safe" perchlorate exposure of about 50 mg/work shift.[9]

Recent volunteer studies have been conducted to determine the exposure level of perchlorate that is associated with small degrees of iodine uptake inhibition. An oral dosage of 10 mg/day perchlorate in water ad libitum for 2 weeks showed a significant inhibition of iodine uptake of 38%, and at 3 mg/day a non-significant inhibition of about 10%.[10,11] These data extrapolate to a no-effect or a threshold of inhibition level of about 2 mg/day. A second laboratory performed similar studies with oral dosages of 35 mg/day, 7 mg/day, 1.4 mg/day, and 0.5 mg/day given in four divided doses in water at specific times over the waking hours.[12] Those researchers demonstrated a no-effect level of iodine uptake inhibition at 0.5 mg/day.

Since July 1997, perchlorate levels in southern Nevada drinking water has been measured by the Southern Nevada Water Authority. Eighty-six measurements were taken of the perchlorate levels in the Clark County drinking water between July 1997 and January 2001. These values ranged from non-detect to 23.8 μg/L (ppb), with a mean of 11.5 μg/L. The mean is 11.6 μg/L if non-detects (ie, <4 μg/L) are assumed to be 2 μg/L in the calculations. The concentration of perchlorate in the Clark County drinking water depends on which thermocline (temperature-stratified water level) is at the intake level of the water tower in Lake Mead, the source of the water. During mid-November 2000 through mid-December 2000, the perchlorate concentration ranged between 21.2 ppb and 23.8 ppb. Nonetheless, the monthly average perchlorate levels from July 1997 through January 2001 have ranged between non-detect and 18.4 ppb, with a mean of 9.6 μg/L (with non-detects = 2 μg/L).

Risk assessments usually assume a daily intake of 2 L. At that rate, the daily perchlorate ingestion in Clark County may be estimated at 19 μg/day (9.6 μg/L × 2 L/day = 19 μg/day). This daily exposure level is lower than the 36 μg/day acceptable under the California advisory action level for perchlorate of 18 μg/L[13] and the 64-μg/day exposure level calculated from the 32-μg/L equivalent of the most recently calculated reference dose of the US Environmental Protection Agency (EPA).[14]

The estimated daily dosage of 19 μg/day for Clark County residents from drinking water is lower than the acceptable daily ingestions of 36 to 64 μg/day, based on the California and EPA guidances, and is clearly orders of magnitude below the tens of milligrams dosages at which perchlorate might adversely affect the level of thyroid hormones thyroxine and thyroid-stimulating hormone. The Crump estimate of 50 mg/work shift absorption for the benchmark dose limit compared with the Clark County resident ingestion of 19 μg/day is a ratio of >2500. Certainly, if these environmental levels were to have caused an increase in one of the thyroid diseases, that increase was unlikely to have been due to a mechanism involving

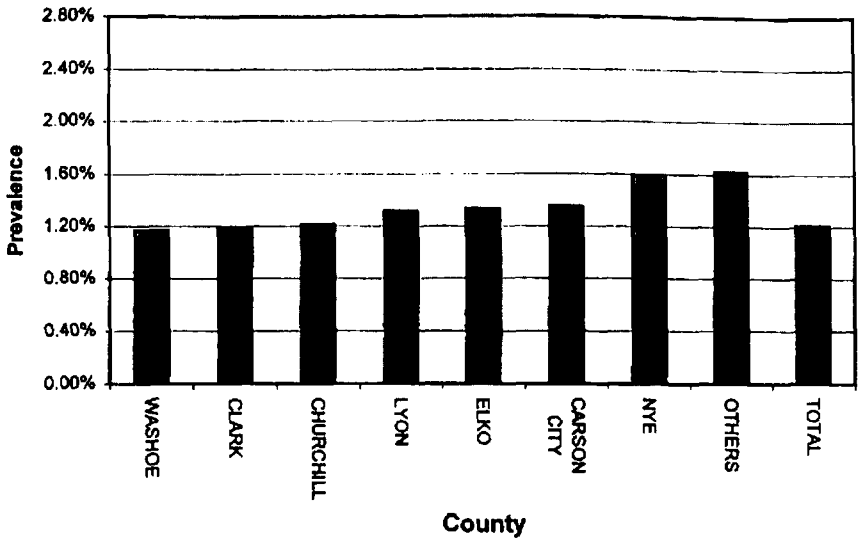

Fig. 2. Prevalence of acquired hypothyroidism (ICD-9, 244) by Nevada counties, January 1, 1997, to December 31, 1998. Clark County is the area with perchlorate exposure.

changes in the circulating levels of thyroxine or of thyroid-stimulating hormone. If the exposure level of 19 μg/day is compared with the exposure range for iodine uptake inhibition (approximately 1 mg/day to 100 mg/day), the ratio is from >50 to >5000. If the exposure level of 19 mg/day is compared with the lowest reported iodine inhibition threshold of 0.5 mg/day, the ratio is still >25. Thus, the a priori prediction would be that such levels of perchlorate are unlikely to elevate thyroid disease rates. Nonetheless, a demonstration is weightier than a prediction.

This study found no increase in the prevalence of any adult thyroid disease associated with the presence of perchlorate in the drinking water in Nevada. The analysis presented is a crude analysis, because age-specific data were not available. Nonetheless, the data have the advantage of being public health data that were collected in the ordinary governmental processes independent of the hypothesis for which they were examined.

Acknowledgments

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